

# Hepatitis B Antiviral Drug Resistance: Navigating the Way Forward

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# Prevention of Antiviral Drug Resistance

# Strategies to Prevent the Development of Antiviral Resistance

## Prevention

Judicious timing of treatment  
Education regarding adherence to therapy



## First line therapy

High potency drug with high genetic barrier to resistance E.g. Entecavir, Tenofovir  
Consider PEG IFN as an alternative first line therapy (eg. High ALT, Low HBV DNA)



## Monitoring

Regular 3–6 monthly monitoring of viral load with sensitive HBV DNA assay  
Genotypic resistance testing in patients with virological breakthrough



## Salvage therapy

Early initiation of “add on” salvage therapy  
Avoid “switch” sequential monotherapy  
Avoid combination therapy using drugs with similar cross resistance profiles

# Summary

- Current emerging patterns of antiviral drug resistance to HBV Pol are complex; But four major pathways can be defined
  - (rtM204V/I;rtN236T;rtA181T/V;ETV [naïve] )
- Primary resistance mutations across NA groups: A181T/V
- Broad clusters of compensatory mutations during Lamivudine therapy (T184G/S202I/M250V Vs rtI169T+rtV173L Vs rtT184S) compromising future salvage therapy options with the newer agents (Entecavir)

# Summary

- Requirement for HBV Pol sequencing to determine profile of antiviral drug resistance
- Emergence of MultiDrug Resistance (MDR) clear cause for concern
- Public health issues around Pol-Env Overlap and vaccine escape
- Need for newer antiviral agents targeted to other sites in the viral life-cycle

# Practice of Continuing LMV Therapy in Patients with LMV Resistance

## Patients with LMV Resistant HBV (rtM204I)

- lower serum ALT compared to pre-therapy
- lower HBV DNA elevations compared to pre-therapy

## HOWEVER

- marked flares of serum ALT are observed
- acute exacerbations in liver disease can occur
- these flares may be followed by HBeAg seroconversion and/or immune clearance of mutant HBV  
(Liaw et al. 1999. Hepatology 30:567)

## BUT

- a new and distinct mutant may be selected and elicit another exacerbation and then select another mutant (rtA181T/V)  
(Yeh et al. 2000. Hepatology 31:1318)

- Further compensatory mutations continue to occur, such as **rtV173L**

(Delaney et al. 2003. J.Virol 77:11833-11841)

and **rtV214A/rtQ215S**.

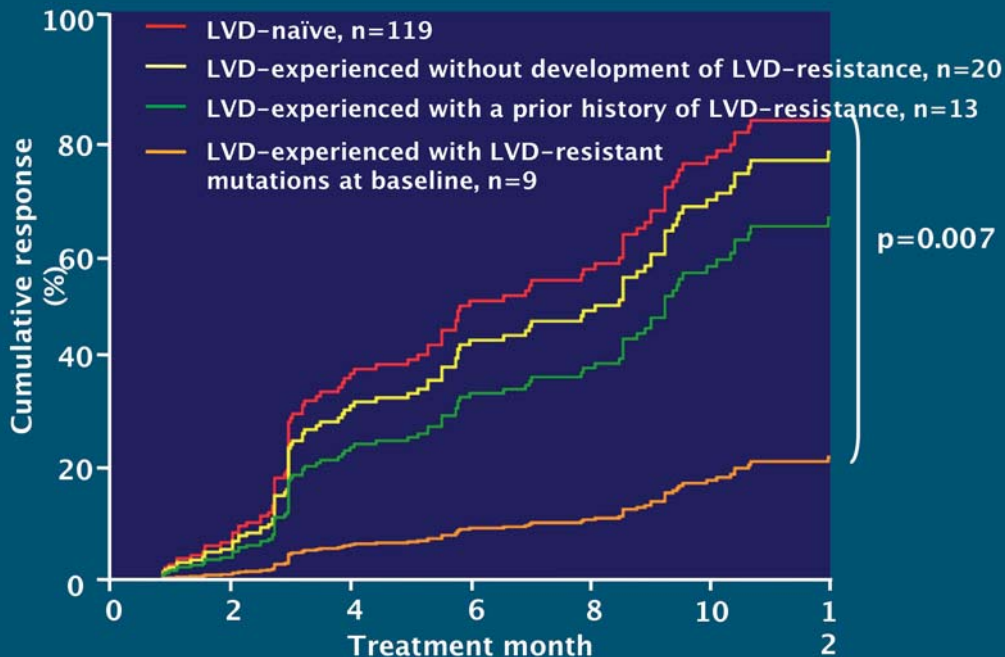
594A)

and **rtT184S**

(Bartholomeusz et al. 2005. Hepatology 42(Suppl.1):

- Which will affect subsequent efficacy of salvage/rescue therapy

# Entecavir: an Option in LVD-Experienced Patients Without LVD-Resistance



# Ways to Prevent Resistance

## Maximize antiviral activity

- increase maximum tolerated dose
- select most effective regimen (combination)
- nucleoside analogue potentiation

## Maximize genetic barriers to resistance

- avoid sequential monotherapy
- choose drugs requiring multiple resistance mutations (1 or 2 mutations pre-exist vs 3 or 4 require ongoing selection)
- choose drugs where patient is naïve

## Increase pharmacologic barriers

- patient compliance
- raising trough levels
- Prior drug experience
- Drug metabolism
- pharmacodynamic issues (eg, cirrhosis)